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Discours de Tomas Hökfelt, lauréat de la Grande Médaille

Monsieur le Président
Messieurs les Secrétaires perpétuels
Mesdames, messieurs

It is indeed an exceptional honour to receive the Grande Médaille, and I express my deep gratitude. It also gives me an opportunity to thank my French colleagues for long standing and stimulating interactions over several decades. Let me also now thank my many coworkers - without them, no progress. And of course my family. I am truly sorry that me wife cannot attend due to health problems.

My professional life has over more than forty years dealt with the chemical brain, in particular the neurotransmitters and their receptors. They, of course, play a fundamental role in neuronal functions, and are apparently deranged in many mental and neurological/degenerative diseases. Many of the medicines used to day aim at correcting such dysfunctions, e.g. in depression. Transmitters and their receptors are also targets for drugs of abuse. Our basic concept has been that knowing the localization of chemicals in the nervous system allows, I am not saying an 'intelligent', but still a 'better' design of experiments to understand their function.

My research started in 1962, when a new professor was appointed in our department of histology at Karolinska, a person who would change neuroscience in Sweden, in fact world-wide, perhaps more than any other Swedish scientist. It was Nils-Åke Hillarp, who together with his student Bengt Falck and actually Arvid Carlsson's, the Nobel laureate's, group in the beginning of the 1960'ies developed a new method, based on formaldehyde-induced fluorescence, that allowed visualization of catecholamines and serotonin in individual cells and nerve fibers – this was the beginning of a new discipline in neuroscience: Chemical neuroanatomy. At Karolinska Hillarp gathered, in a few years, a group of ten young students around him. The first ones to explore the new methodology were Kjell Fuxe and Annica Dahlström who in some pioneering papers described the distribution of the monoamine cells

in the rat brain – a mapping that today is still valid, more than 40 years later. So one thing is good with chemical neuroanatomy, if you do it right, the results have a long half-life. This is the field in which I have worked for now more than four decades. Together with Anders Björklund, the pioneer in the transplantation field, I have edited 21 volumes of the Handbook of Chemical Neuroanatomy which cover many of the advances in this area over the last decades (1983 and 2005).

Hillarp is an excellent example of how a single person can give rise not only to a new field but also to several generations of scientists. This is even more astonishing in view of the fact that Hillarp, tragically, died just three years after his arrival in Stockholm, in 1965, 49 years old. We, his students, got a unique start in our scientific lives – nothing is more important than to start to work with a supervisor who has the correct concept. If not, you can work very, very hard and still not succeed.

My thesis project was however not based on the fluorescence method, but Hillarp assigned to me the task to identify monomine neurons in the electron microscope. Following in the foot steps of Professors Couteaux and Taxi here in Paris, I succeeded, after several years, in showing that monoamines in the brain are stored in the synaptic vesicles, possibly the first histochemical visualization of a transmitter in brain synaptic vesicles. At that time Hillarp had died and thus never got to know that I, in fact, was able to complete my thesis work.

The ultrastructural analysis showed clearly that the monoamines only were present in a small proportion of all nerve terminals. I therefore searched for methods to visualize other transmitters, initially the inhibitory amino acid GABA. In fact, using autoradiography my student Åke Ljungdahl and I were able, for the first time, to identify GABA neurons in tissue sections in some regions of the central nervous system.

Even the Falck-Hillarp method and autoradiography have their limitations, and the introduction of immunohistochemistry in neurobiology meant a revolution. This method, worked out by the late Albert Coons (1912-1978), Professor at Harvard Medical School, already in the early 1940'ies, was until 1969 virtually exclusively used in bacteriology and virology. Then it exploded, the first paper published by an Australian group. A recent search in PubMed under the term 'immunohistochemistry' gave more than 400.000 hits, 99% of which were published after 1970. This reflects the increasing interest in gaining morphological information at the cellular level in all types of biomedical studies.

We were fortunate to collaborate with the late Dr. Menek Goldstein at New York University Medical School who purified all four enzymes in the catecholamine synthesis and raised antibodies. Ever since then antibodies have been the oxygen of my scientific life. Together with Kjell Fuxe we mapped these systems, one novel finding being the demonstration of an adrenaline system in the rat brain.

Another field opened up in the early 1970'ies, when it became clear that neuropeptides represented a new and very large group of transmitter candidates, maybe hundred or so, with even more receptors. We have mapped some of these molecules, and every now and then we observed something interesting. Thus I noted that some noradrenergic neurons in sympathetic

ganglia also expressed the tridecapeptide somtostatin, that is the growth hormone-release-inhibiting hypothalamic factor discovered in Dr. Guillemin's laboratory. This was the first example that a mammalian neuron can synthesize both a classic transmitter, noradrenaline, and a peptide, that is more than one messenger molecule, a phenomenon we often call coexistence. These results evoked interest, since they seemed to go against a popular rule called the "the one neuron – one transmitter hypothesis". They also provided a new view on signaling in the nervous system, and we said that a neuron can speak many languages. Together with my collaborators, in particular my graduate student Jan Lundberg, now head of global research at AstraZeneca, the pharmaceutical company, we explored the functional role of coexistence, demonstrating, for example, differential subcellular storage sites and a frequency-dependent release of amine versus peptide.

Coexistence of transmitters is very frequent, in fact the rule, and can include a fast transmitter like glutamate, a monoamine like serotonin and several peptides. So this is a bit confusing, to say the least, but within a single neuron there is presumably a hierarchy with regard to functional significance of the individual messengers. We are also thinking about therapy. For example, if a neuron releases more than one messenger, is it enough to interfere with an antagonist that only blocks the receptor for one of the messengers? In 1998 a Science paper from Merck pharmaceutical company reported that a substance P antagonist has as good efficacy as an antidepressant of the SSRI type but without side effects. Unfortunately these positive results could not be reproduced in the phase III study. Nevertheless, many clinical tests are on-going, several by Sanofi-Aventis, and we have not given up the hope that a drug acting via a peptidergic mechanism will go into the clinic. Our more recent studies focus on the dramatic phenotypic changes seen after nerve injury and their significance for neuropathic pain, and on a possible role of neuropeptides, in particular galanin, in depression. In fact, I as many colleagues, dream of succeeding in making an important contribution to translational research.

Finally, seeing how much wonderful research is now done world-wide in so many disciplines, I feel quite embarrassed to be recipient of the prestigious Grande Médaille. Even in my own field novel techniques, based on genetic methods and ingenious instruments, have advanced the chemical neuroanatomy at a breath-taking pace. So I am pleased and grateful to receive the Grande Médaille now, before all new work fully overshadows the research done in my laboratory. Thank you so much.